General

Guideline Title

The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage.

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Apr. 18 p. (Green-top guideline; no. 17). [124 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2003 May. 13 p. (Guideline; no. 17).

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 8, 2016 – Metformin-containing Drugs : The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.

Recommendations

Major Recommendations

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Classification of evidence levels (1++ to 4) and grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

What are the Recommended Investigations of Couples with Recurrent First-Trimester Miscarriage and Second-Trimester Miscarriage?

Antiphospholipid Antibodies

D - All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies.

Karyotyping

D - Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s).

D - Parental peripheral blood karyotyping of both partners should be performed in couples with recurrent miscarriage where testing of products of conception reports an unbalanced structural chromosomal abnormality.

Thrombophilias

D - Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S.

Treatment Options for Recurrent Miscarriage

Antiphospholipid Syndrome

B - Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage.

Pregnancies associated with antiphospholipid antibodies treated with aspirin and heparin remain at high risk of complications during all three trimesters. Although aspirin plus heparin treatment substantially improves the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies, these pregnancies remain at high risk of complications during all three trimesters, including repeated miscarriage, pre-eclampsia, fetal growth restriction and preterm birth; this necessitates careful antenatal surveillance. [Evidence Level: 2+]

A - Neither corticosteroids nor intravenous immunoglobulin therapy improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity.

Genetic Factors

D - The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist.

Genetic counselling offers the couple a prognosis for the risk of future pregnancies with an unbalanced chromosome complement and the opportunity for familial chromosome studies.

Reproductive options in couples with chromosomal rearrangements include proceeding to a further natural pregnancy with or without a prenatal diagnosis test, gamete donation and adoption.

C - Preimplantation genetic screening with in vitro fertilisation treatment in women with unexplained recurrent miscarriage does not improve live birth rates.

Anatomical Factors

Congenital Uterine Malformations

C - There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage.

Cervical Weakness and Cervical Cerclage

A - Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should be considered only in women who are likely to benefit.

B - Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance.

B - In women with a singleton pregnancy and a history of one second-trimester miscarriage attributable to cervical factors, an ultrasound-indicated cerclage should be offered if a cervical length of 25 mm or less is detected by transvaginal scan before 24 weeks of gestation.

Endocrine Factors

B - There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.

B - There is insufficient evidence to evaluate the effect of human chorionic gonadotrophin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.

A - Suppression of high luteinising hormone levels among ovulatory women with recurrent miscarriage and polycystic ovaries does not improve the live birth rate.

C - There is insufficient evidence to evaluate the effect of metformin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.

Immunotherapy

A - Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained recurrent miscarriage does not improve the live birth rate.

Immune treatments should not be offered routinely to women with recurrent miscarriage outside formal research studies.

Inherited Thrombophilias

C - There is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia.

A - Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias.

Women with known heritable thrombophilia are at an increased risk of venous thromboembolism. See the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 37a: "Reducing the risk of thrombosis and embolism during pregnancy and the puerperium."

Unexplained Recurrent Miscarriage

B - Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.

Data suggest that the use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted. Furthermore, clinical evaluation of future treatments for recurrent miscarriage should be performed only in the context of randomised trials of sufficient power to determine efficacy.

Definitions:

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.

B - A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Recurrent miscarriage, specifically:

- Three or more first-trimester miscarriages
- One or more second-trimester miscarriages

Guideline Category

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Medical Genetics

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidance on the investigation and treatment of couples with three or more first-trimester miscarriages or one or more second-trimester miscarriages

Target Population

Couples with three or more first-trimester miscarriages or one or more second-trimester miscarriages

Interventions and Practices Considered

Evaluation

1. Screening for antiphospholipid antibodies
2. Peripheral blood karyotyping
3. Screening for inherited thrombophilias
4. Referral to a clinical geneticist
5. Cytogenetic analysis of the products of conception

Management/Treatment

1. Aspirin plus heparin therapy for antiphospholipid antibodies
2. Cervical cerclage (not recommended routinely)
3. Supportive care for women with unexplained recurrent miscarriage

Note: The following interventions were considered but not recommended: progesterone supplementation, human chorionic gonadotrophin supplementation, prepregnancy suppression of high luteinising hormone (LH), metformin supplementation, steroid treatment, immunotherapy, serial sonographic surveillance, preimplantation genetic screening, uterine septum resection, routine TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus, and herpes simplex virus) screening.

Major Outcomes Considered

- Miscarriage rate
- Incidence of abnormal parental karyotype
- Healthy live birth rate following miscarriage
- Prevalence of fetal chromosomal abnormality
- Perinatal survival after ultrasound-indicated cervical cerclage
- Maternal and fetal morbidity and mortality from treatments

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Cochrane Library and Cochrane Register of Controlled Trials were searched for relevant randomised controlled trials, systematic reviews, and meta-analyses. A search of Medline from 1966 to 2010 was also carried out. The date of the last search was November 2010. In addition, relevant conference proceedings and abstracts were searched.

The databases were searched using the relevant Medical Subject Heading (MeSH) terms including all sub-headings. This was combined with a keyword search using 'human', 'female', 'pregnancy', 'abortion', 'miscarriage', 'habitual', 'recurrent', 'randomised controlled trials' and 'meta-analysis'.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Reviewing and Grading of Evidence

Once the evidence has been collated for each clinical question it needs to be appraised and reviewed (refer to section 3 in "Development of

RCOG Green-top guidelines: producing a clinical practice guideline" for information on the formulation of the clinical questions; see the "Availability of Companion Documents" field). For each question, the study type with least chance of bias should be used. If available, randomised controlled trials (RCTs) of suitable size and quality should be used in preference to observational data. This may vary depending on the outcome being examined.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency, and applicability of the evidence base. The methods used to appraise individual study types are available from the SIGN Web site (www.sign.ac.uk/methodology/checklists.html). An objective appraisal of study quality is essential, but paired reviewing by guideline leads may be impractical because of resource constraints.

Once evidence has been collated and appraised, it can be graded. A judgement on the quality of the evidence will be necessary using the grading system (see the "Rating Scheme for the Strength of the Evidence" field). Where evidence is felt to warrant 'down-grading', for whatever reason, the rationale must be stated. Evidence judged to be of poor quality can be excluded. Any study with a high chance of bias (either 1– or 2–) will be excluded from the guideline and recommendations will not be based on this evidence. This prevents recommendations being based on poor-quality RCTs when higher-quality observational evidence is available.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development

The development of guidelines involves more than the collation and reviewing of evidence. Even with high-quality data from systematic reviews of randomised controlled trials, a value judgement is needed when comparing one therapy with another. This will therefore introduce the need for consensus.

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines are drafted by nominated developers, in contrast to other guideline groups such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who use larger guideline development groups. Equally, in contrast to other guideline groups, the topics chosen for development as Green-top guidelines are concise enough to allow development by a smaller group of individuals.

In agreeing the precise wording of evidence-based guideline recommendations and in developing consensus-based 'good practice points', the Guidelines Committee (GC) will employ an informal consensus approach through group discussion. In line with current methodologies, the entire development process will follow strict guidance and be both transparent and robust. The RCOG acknowledges that formal consensus methods have been described, but these require further evaluation in the context of clinical guideline development. It is envisaged that this will not detract from the rigor of the process but prevent undue delays in development.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.

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Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Following discussion in the Guidelines Committee (GC), each Green-top guideline is formally peer reviewed. At the same time, the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) Web site for further peer discussion before final publication.

All comments will be collated by the RCOG and tabulated for consideration by the guideline leads. Each comment will require discussion. Where comments are rejected then justification will need to be made. Following this review, the document will be updated and the GC will then review the revised draft and the table of comments.

Once the GC signs-off on the guideline, it is submitted to the Standards Board for approval before final publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate evaluation and management of couples with recurrent early pregnancy loss to increase the chance for a successful live birth

Potential Harms

- Cervical cerclage may be associated with a high risk of minor morbidity but no serious morbidity.
- Heparin can be associated with maternal complications including bleeding, hypersensitivity reactions, heparin-induced thrombocytopenia and, when used long term, osteopenia and vertebral fractures. Two prospective studies have shown that the loss of bone mineral density at the lumbar spine associated with low-dose long-term heparin therapy is similar to that which occurs physiologically during normal pregnancy.

Qualifying Statements

Qualifying Statements

Qualifying Statements

The Royal College of Obstetricians and Gynaecologists (RCOG) produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available. This means that RCOG guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Apr. 18 p. (Green-top guideline; no. 17). [124 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2003 May (revised 2011 Apr)

Guideline Developer(s)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

Source(s) of Funding

Royal College of Obstetricians and Gynaecologists

Guideline Committee

Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Conflicts of interest: none declared

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2003 May. 13 p. (Guideline; no. 17).

Guideline Availability

Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .

Availability of Companion Documents

The following are available:

- Development of RCOG Green-top guidelines: policies and processes. Clinical Governance Advice No 1a. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 6 p. Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .
- Development of RCOG Green-top guidelines: producing a scope. Clinical Governance Advice No 1b. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 4 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: producing a clinical practice guideline. Clinical Governance Advice No 1c. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 13 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: consensus methods for adaptation of Green-top guidelines. Clinical Governance Advice No 1d. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Feb. 9 p. Electronic copies: Available from the RCOG Web site .

In addition, suggested audit topics are available in section 7 of the original guideline document .

Patient Resources

The following is available:

- Couples with recurrent miscarriage: what the RCOG guideline means for you. Royal College of Obstetricians and Gynaecologists; 2004 Aug. 8 p. Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on October 17, 2005. This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute on January 26, 2012. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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